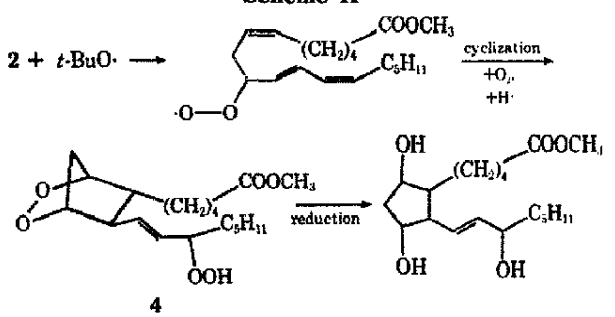
composition of DBPO abstract the labile hydroperoxide hydrogen[3] from 2 giving the peroxy radical. Cyclization of this radical to the endoperoxide followed by reduction[12] leads to PGF-type products.

Scheme II



4

The work reported here lends support to the notion that prostaglandin biosynthesis is a controlled free-radical reaction.[1] Other workers have noted the formation of prostaglandins in autoxidizing lipid.[11,13] The method reported here has the advantage of producing specific peroxy radicals for study as compared to the rather random autoxidation format.

Acknowledgment. This work was supported by grants from NIH and the Army Research Office (Durham). GLC–MS work was carried out at the Research Triangle Institute.

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(11) (a) Our mass spectra were compared to those of compounds obtained by autoxidation of methyl α-linolenate (W. A. Pryor and J. P. Stanley). Fragmentation patterns were generally similar with some exceptions that may be explicable by differences in the proposed structures. We thank Professor Pryor for this information before publication. (b) W. A. Pryor and J. P. Stanley, Abstracts of Papers, American Chemical Society Meeting, Chicago, Ill., Aug 25–29, 1975, paper ORGN-50.
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Received August 15, 1975

A Suggested Mechanism for the Production of Malonaldehyde during the Autoxidation of Polyunsaturated Fatty Acids. Nonenzymatic Production of Prostaglandin Endoperoxides during Autoxidation

Summary: Autoxidation of methyl linolenate is shown to yield materials which give positive tests for both prostaglandin E and malonaldehyde, and it is suggested that both tests respond to prostaglandin-like endoperoxides which can be formed by autoxidation.

Sir: When polyunsaturated fatty acids (PUFA) or esters containing three or more double bonds undergo autoxidation, a material is produced which develops color in a sensitive test with thiobarbituric acid (TBA).[1-9] This TBA test is the most frequently used index of lipid peroxidation both in vitro and in vivo. Although the TBA-reactive material is frequently referred to as malonaldehyde,[5,6,9,10] it has been known for some time[3,4] that this material is predominantly nonvolatile; therefore, it is not malonaldehyde, but rather is a nonvolatile precursor of malonaldehyde.

In 1962, Holman et al.[4] suggested that a five-membered monocyclic peroxide is the nonvolatile malonaldehyde precursor. However, their mechanism does not appear to accommodate all the known facts of TBA-color production during PUFA autoxidation.[1] A more attractive mechanism, in our view, is one in which the nonvolatile malonaldehyde precursor is a bicyclic endoperoxide analogous to that which is formed in the biosynthesis of prostaglandins.[11-20] Figure 1 shows this mechanism as applied to methyl linolenate (18:3). Abstraction of an "internal" allylic hydrogen followed by reaction with O_2 leads to peroxy radicals **4** and **5**. Radical **4** has a structure which allows cyclization to endoperoxide radicals **9**, which are allylic, probably via the oxy-bridged radicals **6**. Radicals **9**, then, can become converted into endoperoxides **10** or **11**.[21-23] Radicals **4** and **5** also can lead to the conjugated hydroperoxides **7** and **8** which are known products of autoxidations.

Our first indication that the nonvolatile malonaldehyde precursor is an endoperoxide came from comparisons of the responses of autoxidized solutions of 18:3 to the TBA test and a test developed for prostaglandin E (PGE).[19,24,25] The PGE test, which involves rapid formation of absorption at 278 nm upon addition of alcoholic base,[19,24,25] probably is relatively unspecific, but it is believed to convert PGE compounds into conjugated dienones such as PGB.[24] Since base is known to rapidly decompose secondary dialkyl peroxides to form ketones and alcohols,[26-28] we expected that endoperoxides, if produced in our autoxidations, would be converted by base into PGE-type compounds. The PGE-type compounds would then react further with base to give PGB-type chromophores and a positive PGE test. It appeared reasonable a priori that endoperoxides could be formed nonenzymatically by autoxidation in our system since the suggested mechanism for their biosynthesis involves a radical cyclization;[11-20] furthermore, Nugteren et al.[29a] have shown that autoxidation of 8,11,14-eicosatrienoic acid gives prostaglandins. Thus, we hypothesized that endoperoxides are produced on autoxidation of 18:3 and are the precursors of malonaldehyde under TBA-test conditions and PGB under conditions for the PGE test. (Note that **10** and **11** should give malonaldehyde but only **11** should give a PGE test.)

Indeed, autoxidized 18:3 does give a PGE test. This is true regardless of whether the oxidation is spontaneous (i.e., effected by pure air), or is initiated[1,2] by ozone or NO_2. On the other hand, 18:2, autoxidized under the same condi-

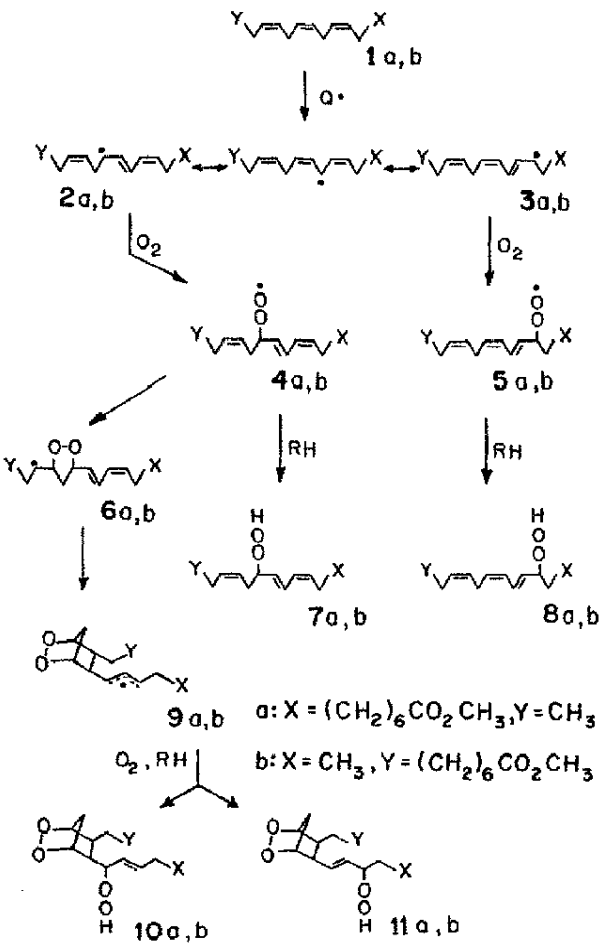

Figure 1. Mechanism for conversion of methyl linolenate to conjugated hydroperoxides and to prostaglandin-like endoperoxides.

tions and to the same degree of reaction, gives either no response or a much lower response to both the PGE and TBA tests.[29b]

When the formation of total peroxidic material, conjugated dienes, and TBA- and PGE-test reactive material is followed as a function of time for autoxidizing 18:3, with added α-tocopherol to produce a significant induction period,[1,2] curves such as shown in Figure 2 are obtained. It can be seen that during the induction period the rates of formation of both TBA- and PGE-test reactive material are very much smaller than the rates of appearance of total peroxide and conjugated diene. These data suggest that the TBA-test and the PGE-test reactive materials have common precursors, namely endoperoxides, which are different from the conjugated hydroperoxide products. [The amounts of PGE material in Figure 2 were calibrated by adding authentic PGE (generously supplied by Upjohn Co.) to our runs.]

The malonaldehyde precursor is a labile peroxide. Shaking an ether solution of autoxidized 18:3 with aqueous $SnCl_2$ not only destroys the peroxidic material (determined iodometrically), but also destroys both the TBA- and the PGE-test reactive material. Partial reduction indicates that the malonaldehyde precursor is reduced faster than is the total peroxidic material. We also have followed the rates of disappearance, during heating under an inert gas, of the total peroxidic materials and the TBA- and PGE-test reactive materials in a sample of autoxodized 18:3.

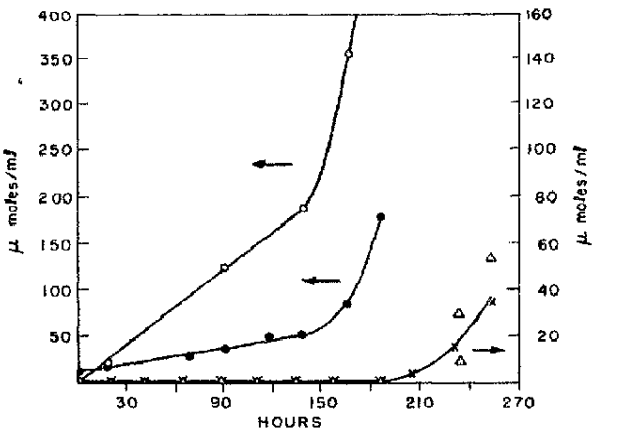

Figure 2. Formation of total peroxide (○), conjugated dienes (●), TBA-test reactive material (×), and PGE-test reactive material (△) with time, during the autoxidation of methyl linolenate containing 1 mg of vitamin E/ml of ester, exposed to 0.25-l./min flow of air containing 1.5 ppm O_3. Left ordinate is for peroxide and conjugated dienes; right ordinate is for TBA-reactive material and PGE-reactive material.

Each of these materials is found to disappear at 80° by a first-order process, with the following rate constants (× 10^5 in reciprocal seconds): total peroxide, 3.4 ± 0.6; TBA, 5.5 ± 2; and PGE, 5.8 ± 1.[30] Although the reproducibility of the rate constants is, for unknown reasons, less than we would have wished, it appears likely that the TBA- and PGE-test reactive materials disappear faster than do conjugated hydroperoxides like 7 and 8. Thus, the former materials cannot be identical with the type of conjugated hydroperoxides, such as 7 and 8, which are the principle hydroperoxides produced.

Although VPC indicates the presence of a large number of product fractions, we have isolated one which appears to contain the reduced and derivatized endoperoxides.[30a] The product mixture from autoxidation of 18:3 was reduced with $SnCl_2$, which converts hydroperoxide into alcohol and endoperoxide into diol,[11,14] and separated into five fractions by silica gel chromatography using cyclohexane as solvent (to remove unreacted 18:3) followed by preparative thin layer chromatography (TLC) using ethyl acetate–isooctane–water, 1:1:2 as solvent. Fraction 1 was subjected to further TLC (50:50 $CHCl_3$–ethyl acetate) into five fractions. The second of these, 1B (R_f 0.22), which represents 81% of fraction 1 and 20% of the total isolated product, was investigated by uv, ir, and NMR spectroscopy. This fraction showed no significant absorbance below 220 nm, indicating that it does not contain a conjugated diene. The ir spectrum reveals very strong alcohol OH stretching, very little if any vinyl hydrogen stretch, and a slightly broadened carbonyl peak. The NMR spectrum indicates that the material is a mixture but is consistent with PGF_1-type compounds being a major component.

Trimethylsilyl and acetate derivatives[14,15,31] were prepared from fraction 1B and the mixture was subjected to gas chromatography–mass spectroscopic analysis. The mass spectra are similar to spectra obtained for similar derivates of $PGF_{1\alpha}$[14,15,32] and to spectra obtained by Porter from cyclization of 6,9,12-octadecatrienoic acid.[33]

There are two major conclusions from the work reported here. The first is that autoxidation of methyl linolenate, and, by extension, other PUFA esters containing three or more double bonds, produces endoperoxides. This finding complements that of Nugteren et al.[29] who found that autoxidation of a trienoic acid gave prostaglandins.[34] It is one

of the basic tenets of free-radical biology that autoxidation of PUFA in vivo, and particularly lipids in membranes, is responsible for important biological consequences.[34,35] The extent to which cyclic peroxides, endoperoxides, and PG analogues, with either natural (i.e., enzymatically produced) or unnatural structures, may be involved in free-radical biology obviously warrants considerable further research effort. The second hypothesis suggested by our work is that PG-like endoperoxides decompose both thermally and under the mild acid catalysis of the TBA test to produce malonaldehyde, and that endoperoxides are the principal nonvolatile precursor of malonaldehyde under our conditions.

Acknowledgment. We are pleased to acknowledge the partial support of this work by NIH Grant HL-16029 and experimental assistance by Dr. E. Blair, Dr. G. Grady, and Dr. W. D. Graham. We also acknowledge with thanks correspondence with Professor Ned Porter.

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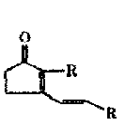

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(30) (a) It is worth stressing that our suggestion that an endoperoxide is the precursor of malonaldehyde (like the previous proposal[4]) is based solely on inferential evidence. Indeed, to date no one has ever isolated any prostaglandin-like endoperoxide from either natural or synthetic sources, although solutions rich in endoperoxides have been prepared.[11,17,22b] All workers, including ourselves, have reduced the endoperoxide in situ before chromatography. (b) The rate constants for the disappearance of the TBA- and PGE-reactive materials (which presumably are those for the decomposition of the endoperoxide under the acidic or basic conditions of these two tests to produce malonaldehyde or PGE) indicate the endoperoxide in our system is more stable than is that from enzymatic preparations. The inherent thermal stability of the 2,3-dioxanorbomane ring system is probably substantial; the biochemical preparations likely contain impurities which catalyze the decomposition.
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Received August 11, 1975

A New Approach for the Stereocontrolled Synthesis of Acyclic Terpenes

Summary: A short stereoselective approach to farnesol, geranylgeraniol, and dimethyl 3,7-dimethyl-(*E,E*)-2,6-decadiene-1,10-dioate based upon the regioselectivity and stereospecificity of allylic alkylation via π-allylpalladium complexes is reported.

Sir: The problems of synthesizing trisubstituted double bonds of defined geometry came to the fore in the squalene problem.[1a] Renewed interest developed as a result of the structural elucidation of the juvenile hormone.[1b] The acyclic polyisoprenoids in general represent an important class of natural products because of their myriad of applications as well as their importance as biosynthetic intermediates. We wish to report (1) an unusual chemospecificity in the formation of π-allylpalladium complexes, (2) a stereoselective approach to acyclic terpenoids[2] involving a direct homologation of simpler building blocks, (3) a new approach to prenylation, and (4) the first application of π-allylpalladium complexes in natural products synthesis.[3]

Treatment of methyl geraniate with palladium chloride under standard conditions[4] (PdCl, NaCl, $CuCl_2$, NaOAc, HOAc, 95°, 68%) gave a single π-allylpalladium complex, mp 117–118°, assigned structure **1**[5] (see Scheme I). The NMR spectrum indicated that the E-α,β-unsaturated system was intact [δ 5.74 (s, 1 H, 2.18 (s, 3 H)] and the stereochemistry of the π-allyl unit was syn [δ 3.75 (s), 3.50 (t, J = 7 Hz), 2.70 (s), each 1 H]. The preference for the nonconjugated double bond is somewhat surprising in light of the importance of the acidity of the abstracted hydrogen on the rate of formation of π-allyl complexes[6] and by consideration of the usual factors affecting stability of the initial olefin–palladium π complex.[7] Thus, π basicity of the olefin appears to be the predominant factor determining this chemospecificity.